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MALIGNANT DISEASE OF THE LARYNX AND PHARYNX

(THIRD COMMUNICATION)

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Introduction

THE two previous reports that were published under the above title in this journal by one of the authors (R.S-H.) dealt chiefly with the results of radiation therapy in malignant disease of the larynx and pharynx. During the last six years cases of malignant disease of the upper air and food passages and the buccal cavity have been treated at the University Röntgeninstitut (Prof. Dr. Schinz) with a technique the principles of which were originally laid down by Coutard. The fundamental technique was christened "Protracted-fractional Treatment" by Schinz and the term has found acceptance in the Anglo-Saxon literature. It is undesirable to apply the term "Coutard" treatment for, as Coutard himself points out, he has developed principles but always refrained from giving a schematic form of treatment. This paper will attempt to explain the technical details and individual modifications of the technique which are, we believe, essential for even a moderate degree of success. The considerations which lead to modification of the treatment are exceedingly important in cancer therapy, whatever the

localization, whatever the type, and whatever method of treatment is used.

Criteria of permanent disappearance of, or "cure" of a carcinoma are not manifest at the time of treatment and even evidence of temporary disappearance is not available, for the effect of the radiation may not be complete until some weeks or even months after the completion of treatment. It is necessary to find some means of knowing when the necessary dosage has been reached during the treatment itself.

The Objects of Radiation Treatment

The death-blow to the "carcinoma-dose" was dealt by the realization of the fact that the effect of radiation varies with the technique.

Certain classical experiments, cited in the first communication, provided the basis for the technique we are about to discuss.

> "By lengthening the time (decreasing the intensity) of irradiation, by decreasing the size and increasing the number of the single doses, it is possible to obtain a differential effect between essential and malignant tissues, by which the malignant tissues will be more effectively destroyed and the healthy tissue will suffer no irreparable damage."

This statement, which is repeated verbatim from the first communication, is as true now as it was then and as it was at the time of its origination by Regaud and Coutard at the beginning of the last decennium. At that time it was regarded as revolutionary but it is now finding general acceptance.

The determination of the optimum degree of protraction and fractionation was the next step. This was and remains an empirical problem based on trial and error, and requires a long time for solution. To start with we divided the dose into fractions of approximately 180 r without specifying the total dose. Two fractions were given daily. The duration of each fraction was protracted from the, at that time, customary few minutes to an hour or more by increasing the filter and the distance from focus to skin.

With this technique no direct signs of a sufficient dose are available and still less is it possible to give a figure for the total dose that is to be regarded as sufficient. We have to

look for subsidiary effects that will serve as a guide for appropriate modifications of treatment during its course and as an indicator for the conclusion of treatment. These subsidiary effects are the *reactions* that may be observed during treatment of all the structures irradiated.

All living structures may show a reaction to X-rays. In its manifestations this reaction is variable from tissue to tissue and from individual to individual. We have to consider the reactions of the following organs :

1. Skin.
   - Epidermis.
   - Dermis.
2. Blood.
3. Salivary and other Secretory Glands.
4. Mucous Membrane.
   - Epithelium.
   - Submucosa.
5. The " Substrate ".
   - Connective Tissue.
   - Capillaries.
   - Muscle.
   - Nerves.
   - Bone.
   - Cartilage, etc.
6. The Neoplasm.
   - Primary Tumour.
   - Metastases.
7. The General Condition.

Finally, strict attention must be paid to possible *inter-reactions* between these groups that may be of vast importance in determining the course and result of treatment.

1. The Skin.

Until comparatively recently the skin reaction was used as a unit of dosage. Acceptance of the fact that the amount of radiation energy necessary to produce a skin reaction varies very widely with the nature of the radiation and the time of its application robbed this form of dosimetry of constancy and the introduction of the physical methods has finally deposed it. The skin is still regarded as being the organ which sets a limit to the amount of radiation that can be employed. This limit

is not found when the radiation technique that we are describing is used. There is, of course, a reaction of the skin which, however, is not irreparable and does not depend directly on the total dose but on the factors of time and rhythm that have been used.

The reactions shown by epidermis and dermis are very different.

(*a*) *Epidermis.* The reaction of the epidermis appears as a rule between the twenty-seventh and thirty-first day of treatment. It begins with a pigmentation of the epidermal cells and is followed by a desiccation. The cells degenerate and are cast off. Desquamation usually occurs on the thirty-fifth day. According to the technique employed, the extent of the degenerative changes may vary. Thus, merely the superficial layers are destroyed to be followed by a dry desquamation—the *radioepidermitis sicca* or the effect may proceed to complete destruction of the epidermis. In this case the epidermis will be shed, leaving the dermis bare—*radioepidermitis exsudativa.* In this case regeneration will take place either from a few more resistant individual epidermal or basement membrane cells that have survived—focal regeneration—or, if absolutely all the epidermal cells have been destroyed, then the regeneration will be peripheral. Regeneration should be complete by the forty-third to forty-seventh day. Provided no permanent damage is done to the dermis, regeneration will always occur. The epidermis is not an organ which, by its reaction, limits the dose.

Nor can the radioepidermitis be regarded as indicating the sufficiency or insufficiency of the dose. Not only are individual variations found in the intensity and course of the radioepidermitis (the fat, the thin, the dark, the fair, etc.), but also no valid relation between the epidermis and other radiated structures can be found. This is particularly true with regard to the tumour itself. The epidermal reaction is an independent phenomenon of relative unimportance. Thus the following course of events may be observed. For a particular tumour a mild rhythm of radiation may be necessary or desirable. On the thirty-fifth day but two-thirds of the total dose have been given. Nevertheless the skin reaction has reached its climax. Radiation is continued without pause. In spite of the continued radiation the epidermis regenerates itself at a rate that cannot be distinguished from the normal. Should

treatment continue another twenty days it is possible to observe a second reaction of the newly developed epidermis.

The reaction of the skin is disagreeable and sometimes painful and must be alleviated, or avoided if possible. Although a profound alteration of the skin reaction might be achieved by modifying the physical conditions of irradiation, it is not possible to use this method, for these conditions are fixed by therapeutic considerations. The adjuvant methods at our disposal are, firstly, the avoidance of all mechanical irritation such as collars and scrubbing brushes; secondly protection with ointments which must be bland and contain no metal, such as vaseline.

We have recently adopted a third adjuvant treatment which promises considerable success. Halkin and Lapière, who introduced *red and infra-red radiations* as a means of reducing the skin reactions, found that there was an antagonistic relation between X-rays and the red and infra-red rays. Subsequently other authors have shown that the action of the red rays is not limited to the epidermis, but extends to the dermis. Above all, the vascularity of the latter is preserved and post-therapeutic vasomotor disturbances are avoided. We carried out investigations in which the more strongly radiated side of the neck was treated twice daily with infra-red and red radiations for seven, increasing to twenty, minutes during the last two to three weeks of X-ray radiation, whereas the other side of the neck was not treated with these rays. We found that the side thus treated, in spite of the higher dose of X-rays, showed a much slighter radioepidermitis than the other side. We now treat all cases in this way and find that the course of the radioepidermitis is less intense and that healing is more rapid. Should, in spite of the infra-red radiation, a *radioepidermitis exsudativa* appear the said radiation is continued until healing occurs. Vasomotor sequelae are prevented. The infra-red and red radiation has, of course, no action of the deeper tissues, mucous membrane or tumour.

(*b*) *Dermis*. Before the commencement of the radio-epidermitis a hyperæmia of the deeper tissues is indicated by the deepening in colour and the increase in temperature of the radiated region. The vasomotor changes sometimes cause a transient primary œdema. Under normal conditions of dosage the changes are at no stage more severe. At the time of

desquamation the surface of the dermis which is exposed weeps a thin serum but does not bleed unless the capillaries, which do not quite reach the surface, are mechanically opened, e.g. in connection with changes of dressing. Equally, provided the surface remains aseptic there will be no frank pus formation and the secretion will be fibrinous. It is not always possible to preserve an absolute asepsis under working conditions and a certain amount of pus formation is then found. It does not delay healing. Infection seems to be prevented by the application of compresses soaked in mixed strepto- and staphylo-coccal vaccines. After re-epithelialization no changes can be detected in the dermis as a rule. Some cases show residual vasomotor disturbances of a permanent or semi-permanent character such as telangiectases or œdema. The appearance of such semi-permanent changes is usually prophesied by unusual delay in the regeneration of the epithelium. Although such changes are not dangerous, we regard them now as the expression of a faulty technique, particularly with regard to the individualization of the rhythm. We see them but rarely now, particularly since the introduction of red and infra-red rays as adjuvant treatment. Permanent destruction of the dermis does not occur, even when the most enormous doses are applied. Thus under experimental conditions 8,000 r, measured in air, have been applied to the skin without permanent damage. This exceeds considerably the 7,000 r regarded by Borak as being likely to produce a radio-necrosis. There does not seem to be a definite maximum dose above which permanent damage will occur, it all depends on the rhythm, the fractionation and, probably, on the protraction. Such permanent damage is characterized by the development of an endarteritis obliterans with gangrene of the dermis and death of the epithelium. The result is a radiation ulcer which may take years to heal and is, in contradistinction to the changes that we have described, invariably severely painful.

The skin reactions, radiodermitis and radioepidermitis are neither an indicator nor a limiting factor in protracted fractional treatment. They are not desirable and should if possible be reduced.

2. Blood Changes.

The blood changes of patients undergoing protracted fractional treatment was the subject of investigations by

Lavedan and by Gloor and Zuppinger. They showed that the treatment may lead to a leucopenia and a relative and absolute lymphopenia. The effect is only marked when large volumes are radiated. It is slight in the case of radiation of the head and neck and it has not been found to be a factor calling for modification of the treatment. The blood condition with its modifications, both those due to the disease and to the treatment, must be regarded as a constituent factor of the general condition of the patient which, as will be shown below, is of primary importance.

3. The Salivary Glands.

The salivary glands are somewhat susceptible to this type of radiation treatment and, although the effects are reversible they do, in fact, sometimes last a long time and are uncomfortable for the patient. Comparatively soon after the commencement of treatment the secretion of saliva is increased, but it remains watery. At about the same time the sense of taste undergoes a perversion. Should the rhythm of treatment not be intense it may be possible to prevent an increase of these symptoms which then rapidly disappear after the conclusion of treatment. It is not uncommon to meet with intensification of the symptoms. The secretion becomes reduced and the saliva becomes thick and viscid. The sense of taste is more or less lost and there remains a feeling of general unpleasantness in the mouth. These events are of importance for they result in a marked loss of appetite which may be exacerbated by the other effects of radiation. The nutrition of the patient is rendered difficult and loss of weight and general condition is the result. The saliva cannot readily be swallowed and is difficult to expectorate. This may be an adjuvant factor in the production of a pneumonia. The alteration of the saliva has a bad effect on the teeth. After the conclusion of treatment there will be an improvement but it may require months before complete recovery takes place.

Treatment is only moderately effective. We are accustomed to give pilocarpine in small doses over a long period which benefits some of the patients. Further, we try to avoid these symptoms or at any rate ameliorate them by attention to the rhythm of treatment.

4. The Mucous Membrane.

Any form of radiation treatment of a growth of the regions in question will, if the treatment is of sufficient intensity to cause a reaction of the growth, also cause a reaction of the epithelium which is, in the majority of cases, the parent tissue of the growth. The reaction presented by the mucosa is characteristic for this form of treatment. Not that the destruction of the epithelium is less than that found in association with other forms of treatment, on the contrary it is, or at least can be, distinctly more intense. The difference lies in the fact that the protracted-fractional technique permits destruction of the epithelium while conserving the vascular connective tissue which forms the mechanical support, provides for the nourishment and is necessary for the regeneration of the epithelium. This tissue corresponds to the dermis although, particularly in the case of squamous mucosa, the line of division is not so precise. The importance of this reaction is to be found *firstly* in the fact that the epithelial reaction, the radioepithelitis, provides an accurate picture of what the irradiations are doing and have done. *Secondly*, the epithelium is, for the carcinomata, the blastological parent tissue of the tumour and the visible effect of the radiation on the epithelium may be correlated with the effect on the tumour (Indicator). *Thirdly*, the subepithelial vascular tissue is not only the "supply service" for the epithelium *but also for the tumour*. The deeper tissues represent the second line of supply service. *Fourthly*, the effect of the reaction on the general condition can be very serious. An inter-reaction between the two may start a vicious circle which can compel an interruption or abandonment of the treatment and possibly cause a treatment fatality.

In our opinion, insufficient recognition of these facts, accompanied by the inevitably insufficient individualization of the time factors in treatment is the most frequent cause of failure, not only of this form of treatment for these types of growth *but also of all forms of carcinoma therapy for all types and localizations of growth.*

The morbid anatomy and the course of the reaction of the mucosa presents a fairly close analogy with that of the skin. The time relations, particularly for squamous epithelium, are very different.

(*a*) *The Epithelium.* The various epithelia that are met with in these regions are not all equally sensitive. This is to be expected in view of their different structure and function. Considering the epithelium of the mesopharynx, which occupies a middle position the warning is given some ten days after the beginning of treatment by vague subjective symptoms, particularly in swallowing. Shortly afterwards the first objective signs appear—loss of shine and hyperæmia. These are properly to be regarded as a reaction of the substrate. Thus, it is shown early and definitely by the epithelium of the hard palate, with its deficient substrate, whereas this reaction is less marked over the soft palate, which has an adequate substrate. Definite signs of the epithelial reaction proper appear between the seventeenth and twenty-first day. A degeneration of the superficial layers of the epithelium, which may commence in the neighbourhood of the tumour, particularly if this is situated in the region of the more sensitive epithelium, is the first sign. Borak has drawn attention to the fact that this stage is signalized by a keratinization of the superficial layers of the epithelium. A true aseptic inflammation of the subepithelial tissue is commencing and the products of this inflammation are, to use Borak's words, " soaked up " by the epithelium, which loses its translucency and is patchily covered by a tenuous white membrane consisting chiefly of fibrin, mixed with migrated leucocytes and shed epithelial cells. Borak describes a regeneration from this point should radiation, having been kept within low limits, now be terminated. This would be an auto-cellular regeneration from the surviving epithelial cells analogous to that seen in *radioepidermitis sicca*. In the majority of cases this will not be the moment to cease radiation and the reaction will progress. It will remain patchy for a few days, showing a variable sensitivity of the individual epithelial cells within the same area. The patches will increase in size and thickness, taking on a grey-green colour, and eventually become confluent. This stage is the culminating point of the reaction and it represents a destruction of the epithelial cells down to and including most of the basement membrane. It is the stage of *radioepithelitis*. The greater part of the radiated region is covered by the membrane, which resembles the membranes seen in a severe diphtheria. Borak describes this membrane as yellow but also compares it to the diphtheroid membranes.

The membrane consists of fibrin and necrotic epithelial cells and replaces the epithelium but not the subepithelial tissues. It should give the impression of being approximately equal to the epithelium in thickness. Thus, the tip of the epiglottis, which is covered by a thin epithelium, should be covered by a thin radioepithelitis through which the red colour of the deeper structures shimmers. Underneath this false membrane a new epithelium is formed and the false membrane is shed. The repair should be complete at each point about two weeks after the commencement of the reaction of that point. *The less intense the reaction, the longer it may be permitted to endure.*

This description of the appearance and course of the radioepithelitis, and particularly of its time relations, is given with reserve. Firstly, there are differences in the reaction of the various types of epithelium which are found in the regions under discussion. Regarding the order of appearance of the reactions as a measure of the sensitivity of the various sections, we find that the epithelia of the uvula and the soft palate are the most sensitive and show an early reaction. The secondary radiation from the vertebral column may cause an early reaction of the posterior wall of the pharynx. This is followed by the pharynx, including the upper part of the larynx but excluding the sinus pyriformis. The latter follow on and show a sensitivity approximately equal to that of the buccal cavity, excluding the tongue. Least sensitive is the epithelium of the tongue and of the deeper part of the larynx (true cord and upper part of the trachea). Practically identical conclusions have been reached by Borak: and Coutard, on the occasion of the opening of the Marie Curie Hospital, emphasized the phenomenon, pointing out that the time relations of the radioepithelitis of the deeper part of the larynx, which commencing about the twenty-sixth day should be repaired by the thirty-ninth, were closely analogous to those of the skin. In our material the skin reaction has been somewhat later than this as a rule, but we have observed the same chronology in the case of the larynx. In some cases traces of the reaction are still visible in the depths of the larynx a fortnight or even more after treatment. It seems that a longer time is required for the repair of the more highly specialized epithelium. Secondly, individual variations are found. The inter-reactions between tumour and substrate vary from case to case.

These variations will be discussed under the section on inter-reactions.

(*b*) *The Subepithelial tissues.*—As in the case of the dermis, the reaction of the subepithelial tissue should be minimal. The tissues are not observable during treatment and we must infer the nature of the changes. These should be limited to reversible vasculomotor reactions. Evidence of this is provided by the hyperæmia that is observable at the beginning of treatment and the œdema that is sometimes observed during and even after treatment ; but we regard the latter, as in the case of the skin, as evidence of a faulty technique. Further, this tissue forms, together with the deeper tissues, the *substrate of the tumour* and has important inter-reactions with the tumour which will be discussed under a special heading.

5. The Substrate.

Of primary and supreme importance in the treatment of a growth is the reaction of the vascular connective tissue and the vascular layer of the mucosa. The reactions of the remaining structures, large blood vessels, muscles, nerves, bone and cartilage are of secondary importance although their manifestations, in isolated instances, may be dramatic and dangerous.

The morbid anatomy and histology of the changes shown by the vascular connective tissues, the nutrient substrate, are not known very exactly for the tissues are difficult of access. From the somewhat incomplete direct observations that are available and from the effects on more accessible structures, the tumour and the epithelium, we may infer that at the beginning of the connective tissue reaction there is a transient hyperæmia which is followed by a stage characterized by a reduction of the nutrient capacity of the substrate. This reduction must under all circumstances be held within the limits after which a recovery is no longer possible ; but the question of the permissible intensity and of the permissible duration of this reaction, with regard to its inter-reaction with the tumour is more delicate.

It is certain that the individualization of the course and intensity of the reaction of the nutrient substrate is of fundamental importance for successful treatment. The reactions shown by the epithelium are a measure and an indicator of substrate changes. The extent of these changes is strongly affected by comparatively slight changes in the radiation

technique. These modifications all lie within the limits of the fundamental technique that we have described and will be discussed in their theory and practice in the section on inter-reactions.

With regard to the other structures, we shall be brief. During the course of the treatment an already eroded blood vessel may be opened, already affected and infected soft tissues, whilst cartilage or bone may occasionally develop a septic spreading cellulitis, a chondritis or infective osteitis followed by necroses with, usually, a rapidly fatal determination. Should a previous infection not be present, such changes are not caused by this technique. Should the infection already be present, then the technique must be modified correspondingly. The necessary modifications can be so extensive that they may render successful treatment difficult and such cases of advanced and deep infection and infiltration are prognostically very unfavourable. Should, in addition, the general condition be indifferent, it is better not to undertake treatment at all, although such a decision, scientifically justifiable, is often difficult in practice.

6. The Tumour.

(*a*) *The Primary Tumour.*—The infinite variety of tumours that are met with in this region, various with regard to their precise localization, extent, macroscopic growth characteristics, degree of surface infection, histology and nutrient substrate, precludes the possibility of even the most schematic generalization of the reaction of the tumour and its metastases. In addition, corresponding to the above characteristics, the treatment may be modified and the tumour reaction will become even less characteristic. Finally there is the unpredictable factor of cancerotherapy. Our purpose will best be served by reporting the following case which, though not in any sense characteristic, nevertheless showed a course that is met with frequently and which was regarded, for this case, as being " according to plan ".

Case I.—H.J. Intrinsic Carcinoma of the Larynx. The patient gave a history of nine months' hoarseness. On examination an ulcerated tumour of the left vocal cord was found. It was the size of an olive, had infiltrated the sinus of Morgagni but was localized to the left side. The left side of the larynx was immovable. No metastases were present. The general condition was good. Histologically : *A moderately differentiated epithelioma of the skin*

type. On the eighth day the tumour showed thin grey-white membranes, covering its surface and localized to the tumour. On the ninth day a slight reduction in size and particularly of the ulceration was noticed. By the twelfth day a further reduction had been noticed. During the following days the tumour appeared to remain constant in size but the developing radioepithelitis rendered accurate examination of the tumour difficult. During the reaction a further reduction in the size of the tumour was noted and at the conclusion of the treatment the tumour could no longer be seen. The left vocal cord showed slight movements. As soon as the reaction had partially subsided it was possible to say definitely on the thirty-sixth day after the commencement of treatment and the seventh day after the conclusion of treatment that the tumour was no longer visible. One month later the laryngeal appearance was absolutely normal. Up to the present, no recurrence.

The dose reached 7,210 r. The dosage is described in detail on p. 255.

This is the course shown by one particular moderately sensitive tumour with no very extensive infiltration. The infected and infiltrating forms show a much longer course. The reduction of the tumour at the beginning of treatment is in such cases minimal or absent. In the early stages a slight reduction in size may be observed but even this is not marked. At the conclusion of treatment, which in such a case will have taken forty or more days, the tumour may still be definitely present. Further reduction will take place after treatment and in a successful case disappearance will occur within a month from the time of conclusion of treatment. The tumour may therefore require from two to three months from the beginning of treatment for its complete disappearance. Even in such cases a successful treatment is followed by only minimal scar building and the presence of *hard residual infiltrations is more often a sign of insufficient sterilization than of scar tissue.*

Occasionally a swelling of the tumour is noticed during the first two or three days of treatment. Tumours threatening to obstruct the airway call for gentle treatment at the beginning to avoid accidents on this account. During the reaction proper we have not been compelled to perform tracheotomy for this cause.

(*b*) *The Reaction of the Metastases.*—The reaction of the regional metastases can in no sense be generalized and is unpredictable for each particular case.

During the first few days of treatment the glands may swell somewhat, as a result of the vasomotor disturbance. This may result in glands that were not previously detected becoming palpable. During the course of treatment a regression will almost certainly be observed. Its amount is very variable and, except in the case of certain very sensitive tumours, it will not be complete at the end of treatment. Regression may continue for several weeks, perhaps up to eight weeks after treatment. Disappearance may be complete. *This is unfortunately far from invariably being the case and it must be admitted that the metastases constitute the most difficult problem.* Residual infiltrations may consist of fibrous tissue and remain stationary for years, but more often there is a suspicion that neoplasm is still present in such residues and the danger of development is very great. It sometimes occurs that glands, inoperable at the commencement, become operable after treatment. It is perfectly possible to remove such glands by operation. The operation may be somewhat more difficult on account of a certain amount of fibrosis but, after correct treatment, this is not serious and the operation is perfectly feasible. It has been carried out for us by the Surgical Clinic, Zürich (Professor Clairmont, and P.D. Dr. Schurch), several times without untoward incidents and with subsequent success. The wound heals normally, per primam. The histological examination of such glands usually shows active carcinoma cells embedded in a mass of fibrous tissue.

7. The General Condition.

The effects of radiation on the general condition are many and important and can, for the greater part, be traced to the reactions of definite organs that have been described above.

The skin reaction as described has no appreciable effect on the general condition. The effect of the minimal blood changes is hardly noticeable. The effect of the reactions of the tumour and the mucosa is very great indeed.

The intracavital reactions are painful, particularly in connection with swallowing. Combined with the perversions of taste there is a loss of appetite, indeed a definite aversion to food and drink. During the reaction it is almost impossible to keep the patient in nutritive balance and loss of weight may reach serious proportions. Losses of four to ten pounds are common and losses of twenty pounds have been observed

in cases in which the rhythm of treatment was not suitable. Such losses may occur in patients already in bad condition as a result of the disease. They may be aggravated by the effects of the absorption from the necrosing tumour of epithelium and are certainly severely increased in the presence of infection. The loss of resistance of the patient consequent upon these effects may reach such alarming proportions that a discontinuation of the treatment is indicated. A super-added comparatively (for normal conditions) slight infection of the lungs may further reduce the general condition and itself progress to an alarming and rapidly fatal pneumonia. These complications are therefore dangerous in themselves and the technique must be directed to their avoidance or at any rate their reduction. Not only are they possibly fatal complications but also a severe reduction of the general condition brings with it alterations of the nutrient substrate. This will lead, firstly, to an increase of the local reactions and hence to the general reaction again, starting a vicious circle and, secondly, *to changes in the nutrition of the tumour which render a successful destruction difficult or even impossible.* These considerations show that it is necessary to keep the intracavital reaction within certain bounds of intensity and duration if a successful treatment is to be concluded. The inter-reaction between the tumour and the general condition occurs through the medium of the nutrient substrate and will be discussed in the following section. The general condition recovers very rapidly after the conclusion of treatment.

The Inter-reactions between Tumour, Epithelium and Substrate

In the early days of radiotherapy it was considered uncertain whether the effect (on the tumour cells) of the radiations was cytocidal or whether the effect was partly due to alterations in the surrounding tissues leading to destruction of the cancer by fibrotic inclusion, nutritional disturbances or the like. This demands a consideration of the radio-sensitivity of malignant growths.

1. Direct Radio-sensitivity.

In the first communication certain types of tumour, according to their histology, were regarded as being highly

sensitive, others less so, and so on, through degrees to those which may be regarded as insensitive. This aspect of radio-histology was discussed at some length and, to recapitulate, we may give the following tumour forms in descending order of radio-sensitivity :

(1) Lymphosarcoma and allied small round-celled sarcomata.
(2) Special form of undifferentiated carcinoma (e.g. Transitional-cell, Cutler ; Lymphoepithelial carcinoma, Schmincke-Regaud).
(3) Undifferentiated epithelioma.
(4) Partially differentiated epithelioma.
(5) Completely differentiated epithelioma.

Although this classification provides a measure of the intrinsic, cytological sensitivity of the growth it is in practice insufficient as a guide to dosage. For the tumours of the last two groups are the most numerous and it is here that vast differences in sensitivity are found. The factors of infiltration and infection overweigh the cytological factors heavily. The presence of these factors, recognizable partly histologically and partly clinically, results in a marked reduction of the success of treatment.

2. The Relation between Tumour Sensitivity and the Radioepithelitis.

In the course of the empirical investigation of the possibilities of the technique it was noticed that success was most often seen in those cases which had shown an early and moderately intense homogeneous reaction. These were the cases showing an exophytic, histologically sensitive tumour. The infiltrating tumours showed an irregular, inhomogeneous reaction in spite of the higher doses which were given with this type. It was concluded that a relation obtained between the tumour cell and the mother tissue with regard to their resistance to radiations. This conclusion, which was rendered more probable by a consideration of the theory of carcinogenesis, has been confirmed in principle by other observers, notably Borak. The subsidiary question, fundamental however for radiation therapy, is whether there is a *difference* in the sensitivity of the tumour and that of the parent tissue. Borak associates himself very definitely with the original opinion advanced by Regaud that the sensitivity of the two is

identical. Admitting that both tumour and parent tissue are composed of cells which vary in their individual sensitivity, he insists that destruction of the tumour cannot be achieved without destruction of the parent tissue, more particularly it is impossible to destroy an epithelioma without destroying the epithelium. He makes an exception for anaplastic forms of carcinoma in view of their exaggerated sensitivity. He further points out that under no circumstances can a tumour be regarded as being *less* sensitive than the parent tissue. As proof of the difference of this type he would demand the demonstration of a complete destruction of the epithelium with incomplete destruction of the tumour. From these considerations he advances the thesis that for the successful destruction of a fully differentiated (sc. resistant) tumour it is invariably and logically necessary to radiate to the point of production of a definite radioepithelitis exsudativa. As before, this thesis will continue to provide an indicator for the radiation treatment of these growths but at the same time the following observations give rise to thought: (1) There are tumours of the resistant infiltrating type that are not destroyed, even when the radioepithelitis has been most intense. (2) Very similar tumours have been successfully treated with a technique that caused a less intense radioepithelitis but which lasted a longer time. (3) Tumours once treated with radiations and recurring are very insusceptible to further radiation treatment. (4) The greater part of a tumour may disappear with a dose that represents but a fraction of that required to sterilize the growth or to produce a destruction of the parent tissue.

As a guide for future investigations we are inclined to adopt the following hypothesis. The "average" sensitivity of the cells composing a tumour bears an approximately constant relation to the "average" sensitivity of the cell of the parent tissue of the same individual. Both tumour and parent tissue contain cells of widely different sensitivity. Since the growth in any case represents a more anaplastic or embryonic form than the parent tissue, the "average" sensitivity is likely to be greater than that of the parent tissue. The more anaplastic or undifferentiated the tumour the larger will be the proportion of highly sensitive cells. Should the tumour be homogeneously anaplastic then all the tumour cells will be more sensitive than the parent cells. This is probably

a rare occurrence. Tumour cells compelled to grow under unfavourable circumstances (infection, infiltrating tumours, etc.) may become more resistant to radiation. This factor does not occur in the case of the epithelial cells and it *may lead to the occurrence of cells within a tumour that are more resistant to radiation than the parent epithelial cells.* Finally, for any given tumour-carrier the magnitude of these differences between tumour and parent tissue is dependent upon the technique of radiation that is employed. The implications and applications of this hypothesis will be discussed under the subsequent headings.

3. Indirect Radio-sensitivity.

It is not possible to destroy the growth without affecting the surrounding substrate at all. In the more resistant types of growth the effects on the substrate are necessarily considerable. They must of course be held within the limits of reversibility or healing would not occur. But the reactions of the substrate have a very profound modifying influence on the resistance of the tumour.

A study of our material has confirmed the conclusions of Coutard that damage to the substrate is a cause of unsuccessful treatment. Apart from the damage that may be caused by radiation, changes in the substrate which reduce its functional capacity are found as a result of infection and above all of infiltration. Other examples of tumour rendered resistant on account of a damaged substrate are the recurrences, both after surgery and after radiology. The disappointing results of treatment of such tumours are notorious.

In a recent paper Coutard has analysed the results of his cases of carcinoma of the hypopharynx up to the end of 1926. During this period the chronology of treatment was not adjusted to this factor of possible resistance. *None* of the tumours which infiltrated the muscle could be cured and only very few of those which infiltrated the subepithelial tissues.

The preservation of the substrate assumes a paramount importance under these circumstances and the whole course of treatment must be designed to prevent damage to the substrate occurring or, if it has already occurred, to prevent its progress and minimize its effect. This is the aim of modifications of the time factor and the rhythm—decreasing the daily

dose and increasing their number—the chronology of treatment.

4. CHRONOLOGY.

The intensity, rhythm and duration of radiation treatment must be designed to achieve destruction of the tumour before the reaction of the substrate has had time to induce a radio-resistance. This object can be obtained either by killing the growth rapidly, or by keeping the damage to the substrate minimal.

There appears to be an optimum time for the destruction of a growth by radiation. This may vary from about twenty days for an undifferentiated, embryonic carcinoma, one hundred days or more for the most resistant types of carcinoma, the latter figure being given by Coutard for certain types of carcinomata. The figure is not only dependent upon the histology of the growth but also on the other factors enumerated above, such as the degree of infiltration.

There may be a maximum time within which it is necessary to complete treatment, to avoid the phenomena described by Regaud under the name radio-immunization. It is possible that these phenomena are but another expression of the necessity for conservation of the substrate. Studies from the Memorial Hospital on carcinoma of the breast show that an *inactive* state can be obtained in which the cancer cells are present but either do not grow at all, or, at the most, only very slowly.

5. INDICATORS.

The object of individualization of treatment is now clear. Since, however, the sensitivity of the tumour with regard to the substrate is a quality that is only approximately capable of determination and the substrate itself is hidden from our examination altogether, it is difficult to choose the correct individualization. The important indicator at our disposal is the observed reaction of the mucosa and, to a lesser extent, the observed reaction of the tumour.

It must first be admitted that there is little or no direct inter-reaction between the tumour and the epithelium from which it has sprung. The destruction of the epithelium does not influence the tumour for better or for worse.

In the case of sensitive exophytic tumours the radio-epithelitis appears early, regularly, and under the influence

of relatively small doses. In spite of this it will be necessary for safety to give an adequate dose and therefore the rhythm of radiation must be somewhat modified to postpone the reaction of the seventeenth to the twentieth day. Owing to the moderate doses that are employed in this type of case, it is not necessary to pay so much attention to the substrate. The technique will be very gentle with the substrate and the reaction of the epithelium will be slight or, corresponding to its sensitivity, of medium intensity. In a tumour which shows no characteristics suggesting a wide variation from a middling sensitivity, the course of the reactions should correspond to that which we have described throughout the paper. Should we have reason to suppose that a resistant tumour is present, then we know in advance that it will be necessary to give a large total dose which, from the point of view of the tumour, may be spread over a longer time and from the point of view of the substrate *must be spread over a long time*. It is therefore necessary to postpone the appearance of the reaction to possibly the twentieth day and, above all, to keep its intensity very moderate. For the reaction may have to be maintained and treatment continued for another twenty or more days.

It will be seen that the attitude adopted at the moment is, for the more resistant types of epithelioma, to lengthen the time, increase the total dose and, by the use of a suitable rhythm, to reduce the reaction of the substrate, a rhythm that must also be designed to emphasize the difference, if any, of the sensitivities of tumour and epithelium. Above all the reaction of the substrate must not be allowed to make the tumour any more insensitive. The increasing realization of the importance of the time factor is resulting in a longer duration of treatment with smaller daily doses. The reaction is less intense. Under some circumstances it is very slight and may be limited to a few tenuous membranes. But even such a slight reaction as this, which is almost without subjective difficulties for the patient, may serve as an indicator for the conduct of treatment. It may be that it will be possible to destroy all these cancers without the production of radio-epithelitis. This point has not yet been reached. It must be emphasized that the reduction in the intensity of the radioepithelitis is associated with an increase in its duration and *an increase in the total dose*.

Malignant Disease of Larynx and Pharynx

The Technique and its Modifications

The foregoing considerations show that an individual technique is required for each case. Nevertheless, certain factors remain constant for all cases and are only modified after employment in a comparatively large number of cases and then usually in connection with changes in the apparatus. These constant factors will be discussed first, to be followed by those that are changed for each individual patient. Finally, certain adjuvant treatments, not radiological, will be considered.

1. The Wave Length of Radiation.

This is controlled by the tension on the tube and the filter. The maximum penetration that the apparatus will deliver, subject to its yielding an intensity of 2·5 r per minute at a distance of not less than 60 cm., is to be chosen on principle. At the moment we are using a tension of 180 kv., a current of 4 ma., and a filter of 2 mm. Cu. + 3 mm. Al. These are the limits of our apparatus. At 60 cm. the intensity is slightly less than 2·5 r per minute, measured in air without back-scattering.

We are convinced that an increase in the tension would be an advantage but are not certain of its extent. Tensions of 350 kv.-600 kv. are now practicable, although somewhat expensive. There is, according to the size of the field, an increase of 10-20 per cent. in the depth dose. This advantage is accentuated by the increased geometrical efficiency, for it is possible to work at a greater distance. This will result in a reduction of the energy that has to be absorbed by the skin and superficial tissues but, since the growths under discussion do not lie very deeply and the skin, even under the present circumstances, does not set a limit to treatment, these advantages are not decisive. (They may well be decisive when the disease is localized in a more deeply seated organ.)

Some observers do not accept the possibility of an increase in the sensitivity of the cancer cells with decrease in the mean wave length of the incident radiation. Their conclusions are based, for the most part, on a series of exact physical measurements, notably by Holthusen, of the following nature. Working with X-rays of varying tension and with radium, he showed that the ratios of the number of röntgens, r, as

measured by a suitable ionization chamber which were necessary to produce certain standard effects (skin-erythema, death to ascaris eggs, etc.) were the same whatever the wave length (sc. tension) employed, *provided the time constants of the irradiation were the same for all test objects*. Falla and his collaborators, working in these and other test objects have brought results which are at variance with those of Holthusen but it must be admitted that Holthusen's objection, that the time constants were different is, to some extent, valid.

The considerations advanced in the first part of this paper show that the aim is not an increase in the absolute sensitivity of the tumour *per se* but to increase the sensitivity of the tumour with regard to the other structures affected. The most important method of achieving this result is the exact adjustment of the chronology of treatment, its length and rhythm to the individual case. But, from McNattin's observations, it is possible to infer that with an increase in the tension the electivity, or relative sensitivity, is more marked, although his paper is primarily concerned with the skin reactions. Berven's results with telecurietherapy in malignant disease of the tonsil show that it is possible to destroy the tumour permanently with minimal reactions of the adjacent tissues, even though the short distance possible leads to a reduction of the geometrical efficiency of the radiation, or depth dose.

The magnitude of the increase in selective action is uncertain, but even if small it is not negligible and further research and clinical application are necessary. But this research must not take place at the cost of neglect of the time factor.

2. Intensity.

We employ an intensity of 2·5 r per minute at 60 cm. distance. This requires, with our apparatus, a tube current of 4 ma. Should larger milliamperages be available, the distance and the filter could be increased with advantage to keep to this order of intensity.

3. Distance.

The distance is regulated to give the individual dose which may vary from 80-250 r in approximately one hour. At 60 cm. one hour is required for 150 r.

The above factors are *not* modified from sitting to sitting except in so far as the distance undergoes a secondary modification according to the dose. Two treatments are given daily.

The Individualization

The size of the field, the dose at each individual sitting, the rhythm of the sittings, and the total dose, are the factors which are individualized for each case, and changed from day to day during the treatment of the same patient.

The last three must be considered together, and it is the spirit rather than the letter of the variations, that we shall attempt to describe.

According to the case, treatment is started with a dose that may vary from 80-160 r which is given twice daily. The resistant tumours and the patients in reduced general condition receive the smaller doses. Should the patient support the radiation well, the doses will be increased after a few days, particularly if the tumour type indicates that there will be no necessity to prolong the reaction unduly. If very long periods of treatment are indicated, it is vital to keep the daily dose low during this period of treatment. At a later stage, the daily dose is altered to accelerate or retard the reaction with regard to the time of its appearance and to modify its intensity. These modifications must be made before the reaction reaches the stage of a radioepithelitis.

The daily dose is, therefore, very subservient to the time during which treatment will be prolonged, which is the controlling factor. The subsequent data must be regarded in this light.

Reverting to the case of intrinsic carcinoma of the larynx, partially described on page 244, we may regard it as representing a case of moderate sensitivity and extent. The tumour was moderately extensive and the situation indicated a rather resistant tumour, but the exophytic type of growth was favourable. The general condition was good. Radiation took the following course :—

A tentative beginning with 2 × 120 r was followed on the fourth day by an increase to 2 × 150 r. On the tenth day not even the preliminary signs of the reaction of the mucous membrane or of the tumour could be found, and the dose was increased to 2 × 160 r. On the following day, a slight but definite decrease in the size of the tumour was noticed. On the sixteenth day a redness of the mucous

membrane (sc. subepithelial tissue) was noticed, and the dose was reduced to 2 × 150 r again. This was continued. Definite membranes appeared on the eighteenth day and they were confluent on the twenty-second. After they had been confluent for four days the dose was reduced to 1 × 160 r daily for two days and then terminated. Total Dose: approx. 8,000 r measured on the surface, 7,210 r measured in air. The radioepithelitis was improving at the time of discharge seven days after the conclusion of treatment.

In this case the rhythm of treatment must be regarded as being towards the upper limit of intensity, the reaction was of moderate duration, thirteen days, whereas correspondingly the total dose is definitely moderate.

If the tumour had been of exceptional sensitivity in relation to a sensitive mucous membrane, then the first signs of the radioepithelitis would have appeared earlier and this would have been a sign for a reduction of the daily dose about the ninth day. Equally, had the tumour shown characteristics pointing to a resistant nature, then a slower rhythm with a higher total dose would have to be chosen. The reaction would have to be later in onset, slighter, and of longer duration. In order to preserve the substrate it is important in a case of this description to commence with comparatively small doses.

Thus, in an infected case of infiltrating carcinoma of the angle between tonsil and tongue treatment may be commenced with 2 × 100 r daily. On the fifteenth day of treatment the dose is increased to 2 × 130 daily. The radioepithelitis may appear about the twenty-fifth day, when the dose has reached 5,000 r. The dose is reduced to 2 × 100 r, or even less, and continued for perhaps twenty or more days. There will be hardly any increase in the intensity of the radioepithelitis during this time, and it will remain very slight. If necessary, this result can be obtained by small daily variations of the dose. The subjective symptoms due to the reaction will be bearable for this comparatively long period. About the thirtieth day, a reduction in the size of the tumour and of the metastases may be observed, the dose being in the neighbourhood of 6,500 r. Treatment is continued until a satisfactory reduction of the primary tumour is obtained which is consistent with the avoidance of a severe effect on the general condition (Weight Curve !). With this type of rhythm a total dose of about 9,000 r or even more may be given with no permanent damage, indeed the healing of the radioepithelitis will be very rapid.

The figures given show the order of magnitude of the dosage and the type of individualization employed and are not to be regarded as a scheme of treatment for any particular case.

Even when comparatively small doses are to be applied we do not reduce the time of the individual dose under fifty minutes but increase the focus-skin distance. This yields an increase in the geometrical efficiency but we feel it is an additional advantage to protract the individual dose. The effect of protraction has been and still is the subject of discussion and we have no clinical experience of results that are obtained by mere fractionation of the dose, a technique that has been adopted by many workers, notably Borak. Theoretically and experimentally, there is a certain lack of unanimity with regard to the effect of protraction. Thus, Borak carried out the following investigation. Two identical parasternal fields were radiated daily with 200 r under exactly the same technical conditions (170 kv., 0·5 mm.Zn.), except that for one field the milliamperage was maintained at 4, whereas for the other field but 1 ma. was used. The individual doses required 12·5 respectively, 50 minutes. Both fields were treated twenty-two times and the total dose was 4,400 r in each case. The difference in the skin reactions between the two sides was minimal. There was a slight delay in the disappearance of the pigmentation on the side that was only fractionally treated without protraction.

On the other hand Holthusen in a series of experiments has shown that the effect of the protraction is by no means negligible particularly with regard to the relative sensitivity of his various test objects. Borak considers that this advantage can be compensated by an increase in the fractionation. At present, following the technique of Coutard we are retaining the protraction of the individual dose for we feel that it is not proved that protraction does not have a better effect with regard to the preservation of the substrate, that is results in an increased *relative sensitivity* of the tumour.

The question is in great need of further, particularly clinical, observation but the latter requires a long time to become conclusive.*

* In our opinion it is exceedingly unjust to regard any difficulties of an economic nature with regard to the application of the principles in question as being of sufficient weight to influence the nature of treatment, c.f. the time and cost of the treatment of tuberculosis in a sanatorium !

The Influence of Metastases on the Course of Treatment

It is clearly essential that fields of irradiation of adequate size must be chosen and must be so arranged that the whole of the primary tumour receives the total dose which is applied. This consideration is sufficient for cases of epithelioma of the larynx which form metastases but exceedingly rarely. For the other localizations the probability of regional metastases and, in many cases, their actual presence complicates the technique of radiation. The fields must be chosen to give an adequate dose to the metastatic area as a precaution when metastases cannot be found and, should they be found, the fields must be large enough to include all the metastases and, if possible, the next barrier of lymphatic glands. This results in fields of very variable size and in some cases very large ones. The reaction of the metastases does not as a rule commence until about the twenty-fifth day of treatment. Therefore not more than about two-thirds or even less of the total possible dose must have been given by this date. A mild rhythm is therefore indicated, particularly at the commencement of treatment. The large fields tend to increase the area of the intra-cavital reaction. It is necessary to commence with smaller individual doses and to proceed to higher total doses when metastases are present. The reaction will be less intense but more prolonged. During the course of treatment it will be desirable to modify the fields employed. It is usually better to reduce them in size at the commencement of the reaction. This makes for difficulties in accurate dosage on account of the back-scattering of the radiations. Since it is the dose including scattering which is effective, it is necessary to determine the secondary radiation. We have been accustomed to measure the dose in air and calculate the back-scattering from the curves of Jacoby and Liechti (First Communication) but this is complicated and inexact on account of the various shapes of field and planes of incidence. Coutard uses a continuous registration dosimeter, the small ionization chamber being placed on the skin and a record being made of each individual dose given including back-scattering. This method is to be regarded as preferable.

Adjuvant Methods of Treatment

It is possible to alleviate the symptoms of the reaction. Food must be light and nourishing, steam kettles, ice-bags,

morphia and atropine and other remedies of a symptomatic nature must be employed, as the case demands.

We have recently adopted another form of adjuvant treatment that has been found extremely promising. Throughout this paper it has been emphasized that all possibilities must be exhausted in an effort to preserve the substrate and its functions. *Ultra-short wave therapy* is of particular assistance in this endeavour. The theoretical basis of its action cannot be discussed here. Practically, U.S.W. therapy results in an increase in the vascularity, the metabolism, and the osmotic changes of the tissues. These effects are particularly marked in the tissues that we have grouped together under the term substrate. The nourishment of the tissues and, therefore, of the tumour is improved. Under these circumstances an increase in the relative sensitivity of the tumour with regard to the substrate is to be expected and our clinical observations have confirmed this expectation.

It seems that only the shorter waves are effective although we have no evidence to prove that the accurate mathematical wave length is decisive. The warmth generated plays a large part in the effect but does not seem to be solely responsible. We have not observed a specific destructive effect on the tumour and the development and appearance of the radioepithelitis is not affected at all. The healing of the radioepithelitis appears to proceed more rapidly in cases thus treated.

From the time of the commencement of the radioepithelitis, or earlier if the case is infected, U.S.W treatment is given, starting with seven minutes increasing to twenty, in some cases longer. As far as possible U.S.W. treatment is given before the X-ray treatment. The electrodes, each about 20×30 cm., are placed on each side of the neck, and the intensity is regulated according to the subjective feelings of the patient; this being as warm as he can tolerate. The U.S.W. therapy is terminated at the same time as the X-ray treatment.

The results are twofold. Subjectively the patient is more comfortable, pain is reduced, swallowing is improved and sleep more easily obtained. These effects may last up to twenty-four hours. Objectively, the infection is reduced, necrotic material and membranes are shed from the tumour, which becomes clean and, often for the first time, accurately

visible. At the same time any œdema of the soft tissues is reduced, an effect which is particularly advantageous in the case of tumours situated low down in the pharynx or in the larynx.

This objective improvement is lasting and, with it, the general condition is improved. These two advantages are not confined to the primary tumour. We have found that the response of cases with regional metastases is markedly improved by this form of adjuvant treatment, although how far there may be a primary or secondary effect on the tumour is uncertain.

Finally the chances of severe complications are reduced. A threatening necrosis may be avoided and we have found it possible to treat cases with infection and threatened necrosis of cartilage and other treatment which, without the U.S.W. therapy, have had to be regarded as being unsuitable for treatment. It should be noted that the benefits of this form of adjuvant treatment are not confined to cases of malignant disease of the regions under discussion. All types of infected tumour have been treated with encouraging results.

Summary

Two previous papers in this *Journal* on malignant disease of the larynx and pharynx dealt almost exclusively with the results of protracted fractional treatment at Zürich. In this paper an attempt is made to describe the technique of treatment as practised at the present moment. The reactions of the various tissues have been discussed. The skin reaction is not a limiting factor, nor is it an indicator for treatment. The skin reaction is reduced or prevented by the application of red and infra-red rays. The reactions of the blood, salivary glands, blood vessels, nerves and muscles are but rarely decisive factors in the treatment. The reaction of the mucous membrane is important as an indicator and, in view of the effect of this reaction on the general condition, the reaction of the *substrate* tissues is of supreme importance. Damage to the substrate, either by the tumour or by the treatment, leads to a reduction in the relative sensitivity of the tumour. Infiltrating and infected tumours, recurrences, and incompletely treated tumours begin with a damaged substrate and are resistant to treatment. The technique must be modified in accordance with the relative sensitivity of each individual

case. The more resistant a tumour the slower is its reaction to radiation and the longer must treatment be continued. This time factor may vary from 20 to 100 days. The size of each individual dose and the total dose are dependent upon this time factor. The time factor must also be chosen to avoid the possibility of further damage to the substrate and a further reduction in the relative sensitivity of the tumour. It will therefore be subject to modifications during the course of treatment, from day to day according to the reactions, local and general, presented by the patient. A long time factor and large fields demand slight local reactions, therefore small individual doses. At the same time the intensity of the radioepithelitis is reduced, preserving the general condition. We are not yet able to dispense with the radioepithelitis as an indicator. The subjective and objective effects of the radioepithelitis are greatly relieved by the use of ultra-short wave therapy.

Only when the treatment is exactly suited to the substrate and the tumour will this form of treatment be relatively safe and attended by encouraging results.

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Diese Arbeit bildet die Fortsetzung von zwei früheren des gleichen Verfassers und betrifft die Ausführung der Technik der gegenwärtigen Behandlungsweise. Dabei wird hervorgehoben, dass die Schleimhautreaktion eine wichtige Indikation darstellt. Neben der Wirkung dieser Reaktion auf den Allegmeinzustand ist auch die Reaktion der umgebenden Gewebe von grösster Wichtigkeit. Eine Schädigung des Grundgewebes durch die Geschwulst oder durch die Behandlung führt zu einer Verminderung der relativen Strahlenempfindlichkeit des Tumors. Infiltrierende oder infizierte Geschwülste, Rezidive oder unvollständig behandelte Geschwülste führen sehr frühzeitig zu einer Schädigung des umgebenden Gewebes und lassen sich durch die Behandlung nicht beeinflussen. Die Technik muss in jedem einzelnen Fall der relativen Empfindlichkeit entsprechen. Nur wenn die Behandlungsart sowohl für das Grundgewebe als auch die Geschwulst selbst genau eingestellt ist, wird sie verhältnismässig gefahrlos und erfolgreich sein.

. . . .

Cet article fait suite à deux autres du même auteur et traite surtout de la technique actuelle du traitment. Il fait ressortir l'importance de la réaction de la muqueuse comme signe indicateur, et en raison de l'effet de cette réaction sur l'état général, la réaction des couches profondes des tissus est d'une très grande importance. Les lésions des couches profondes, produites, soit par la tumeur, soit par le traitement, aboutit à la réduction de la sensibilité relative de la tumeur. Les tumeurs infiltrantes et infectées, les récidives et les tumeurs incomplètement traitées, débutent avec un substratum lésé, et résistent au traitement. La technique doit être modifiée conformément à la sensibilité relative de chaque cas. Ce n'est que lorsque le traitement est exactement adapté au substratum et à la tumeur que cette forme de traitement sera relativement sûre et sera suivie de résultats encourageants.

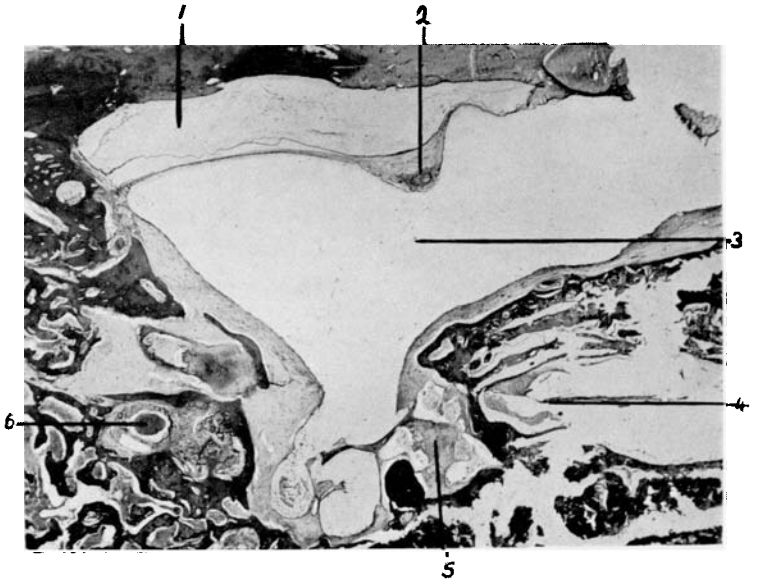

Fig. 1.

Horizontal Section of Middle Ear. × 8.

(1) External acoustic meatus.
(2) Tympanic membrane with handle of malleus.
(3) Middle-ear cavity.
(4) Cochlea.
(5) Niche of round window.
(6) Facial nerve.

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